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Abstract

Background: Bisphenol-A (BPA) is a high production volume chemical used to make polycarbonate plastic that is found in many consumer products. Some studies using animal models have suggested BPA exposures may have adverse health effects. However, research gaps have precluded a full understanding of the effects of BPA in humans and engendered controversies surrounding the chemical's potential toxicity.

Objectives: The National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP) have developed an integrated, multipronged, consortium-based approach to optimize BPA-focused research investments to more effectively address data gaps and inform decision making.

Discussion: NIEHS/NTP BPA research investments made over the past four years include extramural research grants, establishment of a BPA Grantee Consortium, intramural research activities on BPA's mechanisms of action, launch of two clinical studies and an occupational study, development of a round robin experiment to validate BPA measurements in human serum, and, in collaboration with the Food and Drug Administration (FDA), formation of a consortium to design and execute a chronic toxicity study of BPA in rats. NIEHS's new consortium-based approach has led to more integrated, collaborative efforts and should improve our ability to resolve controversies over the potential human health effects of exposures to low levels of endocrine active agents.

Introduction

Bisphenol-A (BPA) is used to produce polycarbonate plastics, epoxy resins, and other products. Manufacturers produce more than 8 billion pounds of BPA every year, making it one of the most common industrial chemicals produced worldwide (Rubin 2011). Plastics made with BPA are used in many consumer products, including food and beverage containers, toys, eyeglasses, computers, kitchen appliances, and medical equipment. Epoxy resins containing the chemical are used in dental work and in metal coatings for food cans, pipes, cars, dairy equipment, office equipment and other metal products. BPA is also used in the production of certain flame retardants and as a color developer in some thermal receipt paper.

BPA has been detected in air, soil, water, landfill leachate, and the human body. The primary source of human exposure to BPA is thought to be through the diet. The chemical has been shown to leach into foods and beverages from food packaging and reusable containers (Von Goetz et al. 2010). People also may be exposed to BPA through skin contact, inhalation, dental fillings, and occupational exposures. BPA has been found in human serum, milk, saliva, urine, and amniotic fluid (Vandenberg et al. 2010; Vandenberg et al. 2012; Vandenberg et al. 2009).

The ubiquity of BPA in the environment and in the human body has led to concerns about adverse health effects. BPA's chemical structure (see Supplemental Material, Figure S1) allows it to fit in the estrogen receptor binding pocket, and BPA is considered to act as an endocrine disruptor. BPA binds to both nuclear and cell membrane estrogen receptors; at higher levels, BPA acts as an androgen receptor antagonist and interacts with the thyroid receptor (Vandenberg et al. 2009). Animal and human research has associated BPA with many health problems including infertility, weight gain, behavioral changes, early-onset puberty, prostate and mammary gland cancers, cardiovascular effects, and diabetes.

Impetus for NIEHS's Strategic Focus on BPA

More than 800 studies were published on the health effects of BPA between the mid-1990s and the mid-2000s. Many showed some form of toxicity, but critical data gaps and uncertainties led to discussion about how the research should be interpreted. In response to increasing concerns about BPA toxicity, NIEHS began developing a targeted BPA research program in the mid-2000s.

As a first step, NIEHS organized a workshop to examine the body of evidence related to BPA. The resulting report, known as the "Chapel Hill consensus statement," published in 2007 along with five review articles (Crain et al. 2007; Keri et al. 2007; Richter et al. 2007; Vandenberg et al. 2007; vom Saal et al. 2007; Wetherill et al. 2007), concluded that human exposure to BPA is widespread and that the adverse health effects observed in animal studies raised significant concerns about the potential for similar effects in humans (vom Saal et al. 2007). It also outlined research gaps and needs.

Around the same time, the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) convened an expert panel to examine BPA research related to human reproduction and development. Based largely on the panel's assessment (Chapin et al. 2008), the NTP reported *negligible concern* for reproductive effects in non-occupationally exposed adults and *minimal concern* for occupationally exposed workers, but identified *some concern* for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current levels of human BPA exposure (NTP 2008).

In 2010, FDA, which has regulatory authority over many consumer and medical products containing BPA, issued a statement expressing its agreement with the NTP's conclusion for some concern about the effects of BPA on the brain, behavior, and prostate gland of fetuses, infants, and children (FDA [Food and Drug Administration] 2012). FDA also identified substantial uncertainties in BPA research findings and their implications for human health. The statement called for further research to address these uncertainties; in the interim, FDA encouraged consumers and industry to take "reasonable steps" to reduce human exposure to BPA, particularly among infants. In March 2012, FDA denied a petition from the Natural Resources Defense Council to revoke regulations permitting the use of BPA in food contact materials, citing insufficient evidence that BPA is unsafe at current levels of human exposure (Dorsey DH [Food and Drug Administration] 2012).

The Chapel Hill consensus statement, the NTP-CERHR monograph, and FDA's statements have helped to focus the field by identifying gaps in BPA research and highlighting concerns that need to be addressed to move the field forward. Key sources of uncertainty that have been identified include: absent or inconsistent data on dose response including low-dose effects and non-monotonic dose response behaviors; pharmacokinetics across species and the lifespan; gender differences; routes and extent of human exposures; sensitive windows of exposure; mechanism(s); and specific disease endpoints. In addition, these reports cited difficulties extrapolating data from animals to humans and comparing results from studies compliant with good laboratory practices (GLP) with academic investigator-initiated studies.

NIEHS BPA Research Program

Because much about the potential health effects of BPA remained unknown, NIEHS determined that a strategic research investment in BPA was warranted in order to better inform risk assessments for the ubiquitous chemical (Maffini et al. 2011). To that end, in 2009 NIEHS launched a multipronged research program designed to fill remaining data gaps and resolve controversies about the design and interpretation of BPA toxicity studies. The plan included significant extramural and intramural research investments, as well as intra- and interagency coordination and collaboration. Elements of NIEHS's BPA research program are described below and summarized in Figure 1. The extramural program's efforts to address specific BPA research challenges are summarized in Supplemental Material, Table S1. NIEHS established a trans-agency working group with members from each of its research divisions (intramural research, extramural research, and NTP) to facilitate coordination of these efforts.

Extramural Research Grants and the BPA Grantee Consortium

By 2008, NIEHS had funded 39 grants to assess BPA toxicity, all of which were investigator-initiated. In 2009, NIEHS awarded 10 BPA-focused Grand Opportunity (GO) grants (see Supplemental Material, Table S2) and three Challenge Grants using funds made available through the American Recovery and Reinvestment Act (ARRA). The ARRA-funded grants were specifically targeted at addressing data gaps identified by FDA, including: measurement of BPA in serum, evaluation of dose response, measurement of disease endpoints, replication of results, assessment of gender-related differences, and use of overlapping endpoints among animal studies and between animal and human studies.

To work toward a comprehensive, integrated assessment of the health effects of BPA, NIEHS brought existing BPA grantees together with the new ARRA-funded grantees into a BPA Grantee Consortium starting in 2009. The consortium includes more than 40 researchers; members have gathered three times in person and met approximately once per month via conference call from late 2009 through the present. This frequent communication has facilitated close collaboration and free exchange of ideas, materials, tissues, and data. Specific activities and areas of focus include the following:

Improved integration of studies: Efforts to extrapolate results between animal and human studies have been complicated by disconnects among the doses and endpoints investigated. Related research gaps include the mechanisms and speed with which BPA is metabolized and excreted in the human body and whether humans and animals process BPA in the same way.

To fill research gaps, resolve discrepancies, and produce results that will be more interpretable across studies, consortium members have worked to establish consistency in the models, approaches, doses, and endpoints used across the spectrum of NIEHS-funded BPA research. In addition, grantees were required to use BPA provided by NIEHS to ensure quality control and consistency. Studies using mice, rats, rhesus monkeys, and humans were coordinated to develop an integrated assessment of BPA metabolism across species; some of these results have already been published (see http://www.niehs.nih.gov/news/sya/sya-bpa/bpa-related/index.cfm). In addition, the NIEHS/NTP clinical pharmacokinetic study (see below) will provide information about the rates of BPA metabolism in human volunteers. The results of that study, combined with the contributions from the BPA Grantee Consortium, will further clarify how data from different animal models may be used to understand and predict health risks in humans.

Round robin assessment of BPA in human serum: The ability to accurately measure exposure to BPA is critical to assessing the chemical's health effects. Measuring BPA in urine is generally considered the most reliable indicator of BPA exposure because it integrates exposure over a recent time period, whereas BPA concentrations in blood are thought to reflect only current exposures due to the chemical's short half-life and evidence that BPA does not bioaccumulate. However, serum measurements are currently the most meaningful way to assess levels of unconjugated BPA (also known as free BPA, which is the form that is considered to be more biologically active because it can bind to estrogen and other nuclear receptors) (Ye et al. 2011). This is an area that requires further investigation because some posit that rapid processing of BPA in the liver during "first pass" metabolism results in only conjugated (and thus biologically inactive) BPA entering the bloodstream, precluding BPA from causing disease. However, more than 30 reports have shown human blood levels of BPA in the range of 0.1-4.0 ng/ml (Taylor et al. 2011; Vandenberg et al. 2010). Although in some cases consistent results have been reported across studies, these findings have spurred debate in the scientific community about the possibility for measurements to be compromised by contamination. For example, small amounts of BPA may leach into samples from syringes, containers, tubing, or even water used in experiments. In addition, instruments used to measure levels of BPA may be incorrectly calibrated.

NIEHS provided supplemental funding to address these controversies through a series of round robin experiments. Members of the BPA Grantee Consortium from five laboratories are measuring BPA levels in a shared collection of uncontaminated blood samples and samples spiked with various amounts of free and conjugated BPA (BPA-glucuronide, -sulfate, and coded samples were provided by NIEHS to ensure quality control). Participating laboratories are also assessing potential sources of contamination and error in their research protocols. Once the experiments produce comparable results and show how to eliminate contamination and other errors, the protocols will be shared for others to use (Dekant and Volkel 2008).

Characterization of low-dose effects: Another factor contributing to uncertainty in BPA research stems from inconsistencies in the characterization of low-dose effects. Studies in both animals and humans have indicated effects of BPA both at low (nanomolar or lower) and high (micromolar or higher) doses, often with fewer effects at mid-level doses (Vandenberg et al. 2012). Such non-monotonic (U-shaped) effects curves may reflect BPA activity in different systems, with low doses causing effects in the endocrine system and high doses potentially causing effects in another organ system. Other studies have reported effects at very low doses but have not included higher doses, making the dose-response relationship difficult to characterize.

In addition, the definition of "low dose" for BPA exposure has led to some debate within the research community. The 2008 NTP-CERHR report defined a "low" dose as ≤ 5 mg/kg bw/day (NTP 2008). However, members of the scientific community have suggested basing the "low dose" designation on levels administered to animals that produce blood levels in the range of what has been measured in human tissues and fluids (0.1-4.0 ng/ml) (Vandenberg et al. 2012).

The BPA Grantee Consortium has provided a forum for discussion about low-dose effects, and through their individual research efforts, consortium members have investigated the effects of low doses of BPA in mice, sheep, and monkeys on multiple disease endpoints. In addition, grantees of the CLARITY-BPA program (see below) are collaborating on a GLP-compliant toxicity study over a wide range of administered BPA doses in rats.

Improving precision for measuring BPA exposures: Human epidemiological studies provide valuable information about the internal levels of human exposure to chemicals and resulting health impacts. Although the National Health and Nutrition Examination Survey (NHANES)

(Calafat et al. 2008; Stahlhut et al. 2009), a statistically-based sampling of the American population conducted every two years, and several birth cohorts, such as the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study cohort (Castorina et al. 2010), have contributed useful data on BPA exposure and impacts, the design and methodology of these studies make it difficult to draw conclusions from them about BPA's health effects (Stahlhut et al. 2009). One reason is that most epidemiological studies have collected urine samples from participants based on convenience rather than at specific time intervals or times of day, making it difficult to compare levels of BPA exposure among samples and participants. In addition, the mechanisms and speed with which the body processes BPA after oral exposure are poorly understood, making it difficult to assess BPA exposure based on measures of BPA conjugates in urine. Potential contamination of samples from laboratory equipment or water containing BPA is also a concern (Vandenberg et al. 2010).

The BPA Grantee Consortium has aimed to address these issues by developing standard protocols and approaches for measuring BPA exposure in humans. Future epidemiological studies can be optimized for BPA research by including serum samples in the study protocol, standardizing time intervals for sampling, and ensuring that all equipment is properly calibrated and BPA-free. The round robin assessment of BPA in serum and the NIEHS/NTP pharmacokinetic study (see below) will provide further insights to inform approaches to detecting BPA exposure levels in humans.

Comprehensive assessments in targeted areas: Consortium members established subgroups to characterize and coordinate research in the following areas: biomonitoring, pharmacokinetics, reproductive effects, cancer, metabolic effects, neurobehavioral effects, low-dose effects, and immune effects. Each subgroup is surveying results published since 2007 and adding data emerging from consortium members' ongoing studies to assess the strength of the evidence in these areas of investigation. The results of these literature-based assessments are expected to be reported as a series of manuscripts in early 2013.

Third-party evaluation: NIEHS has enlisted the aid of the Battelle Centers for Public Health and Evaluation (http://www.battelle.org/solutions/?Nav_Area=Solution&Nav_SectionID=12) for an independent assessment of how ARRA-funded research investments have affected the direction and outcomes of NIEHS's BPA research program.

CLARITY-BPA Program

Findings from studies conducted in accordance with good laboratory practices (GLP) are often used to inform regulatory decision making for potentially harmful chemicals. A number of past animal studies designed in accordance with GLPs have examined the toxicity of BPA (Tyl et al. 2008; Tyl et al. 2002). Although these studies have made valuable contributions, some gaps remain with regard to the exposures and endpoints that have been investigated. For example, no GLP-compliant studies on chronic BPA exposure have included developmental exposure with direct, rather than lactational, exposure of pups. In addition, none have evaluated the internal doses of BPA that are associated with health effects, and these studies have not evaluated several disease endpoints that, although not traditionally included in GLP studies, have been linked to BPA exposure by other animal and human investigations (Myers et al. 2009).

To validate previous findings and address remaining research gaps, the NIEHS/NTP has collaborated with FDA to establish the Consortium Linking Academic and Regulatory Insights on BPA Toxicity to advise the design and execution of a comprehensive GLP-compliant study of BPA toxicity in rats (the "CLARITY-BPA program"). The study, to begin in summer 2012, will be conducted at FDA's National Center for Toxicological Research (NCTR). The strain of animal, animal diet and housing conditions, numbers of animals, dosing regimen, and route of exposure to BPA will be tightly controlled.

To enhance the capacity of this study to provide useful data on a broad array of relevant disease endpoints, a consortium of researchers has been formed that includes 12 grantees who have proposed hypothesis-driven mechanistic studies that have been accommodated within the study design (see Supplemental Material, Table S3). Grantees have also been involved in determining the protocols for the overall study. Although all the animals will be housed and dosed at the NCTR, grantees will have access to tissue samples and animals from the GLP-compliant study to investigate specific disease endpoints, many of which are not typically assessed in studies carried out according to standard regulatory guidelines. To protect the integrity of the GLP study, all researchers will be blinded to the BPA exposure levels of the animals and tissues, with identifying codes housed at NTP. In addition, NTP will provide advice as needed for statistical analyses, and will provide for a common data repository (Chemical Effects in Biological Systems [CEBS] (http://www.niehs.nih.gov/research/resources/databases/cebs/index.cfm)).

The consortium represents an unprecedented approach to conducting GLP-compliant research by bringing researchers and regulators together during the planning stage to ensure results will be maximally useful for risk assessment and regulatory decision-making. The grantees and FDA representatives, along with coordinators from NIEHS/NTP, held their first in-person meeting in March 2012; the collaboration is expected to produce a robust and valuable body of work on the effects of BPA in rats, a key animal model in toxicity testing.

Intramural Research Activities

Illuminating how BPA interacts with receptors in the body is an important aspect of understanding the chemical's toxicity. NIEHS's Division of Intramural Research (DIR) has made significant investments in studying the patterns of response and molecular mechanisms of BPA and other potentially estrogenic chemicals. In experiments using mice, (Hewitt and Korach 2011) used microarrays to compare BPA to other estrogenic compounds and found that BPA could be classified as a weak estrogen, similar to estriol. DIR researchers are also conducting research on BPA's interactions with estrogen receptors α and β in human cell lines, developing *in vitro* and *in vivo* screening tools to gauge estrogenicity that could be used to test BPA, and collaborating with extramural grantees on BPA research using non-human primates. These efforts aim to further advance scientists' ability to evaluate modes of action and mechanisms of BPA and other potentially estrogenic chemicals.

NIEHS/NTP Pharmacokinetic Study

Consumption of canned foods and beverages is thought to be a major route of human exposure to BPA, and (Teeguarden et al. 2011) were able to detect measurable blood levels of total (free and conjugated) BPA in a small fraction of individuals consuming a diet heavy in canned foods and juices; however, only one study has directly examined the kinetics of BPA metabolism and elimination in human volunteers given measured amounts of BPA orally (Völkel et al. 2002), and that study used analytical methods that were less sensitive than current techniques (Vandenberg et al. 2010). Thus, because our understanding of human pharmacokinetics remains limited, to further elucidate how BPA is processed in the human body, the NTP and the NIEHS Clinical Research Unit have developed a protocol to investigate BPA metabolism and excretion in humans after oral ingestion. Up to 50 healthy adult volunteers will be administered a low dose of deuterated BPA (d-BPA) to support development of a refined physiologically-based pharmacokinetic model. Participants will receive 100 µg of d-BPA per kg of body weight by oral administration; blood (starting at 10 minutes) and urine samples will be collected for five days following dosing to measure d-BPA and d-BPA conjugates. By assessing how the body processes and excretes BPA, the study aims to inform investigations of human exposure to BPA and the chemical's potential toxicity. Combined with extramural research on BPA pharmacokinetics in animal models, the study will further elucidate how BPA is processed in the body and help improve researchers' ability to integrate animal and human studies.

NIEHS/NTP Cashier Study

Another source of uncertainty regarding human exposure to BPA is the potential role of sources of exposure other than diet. Because BPA is used in numerous consumer products and industrial processes, inhalation and absorption through the skin have been proposed as potentially significant routes of exposure (Liao and Kannan 2011). For example, it has been proposed that people may inhale or ingest BPA through house dust, or inhale it through smoke from cigarettes with filters containing BPA (Von Goetz et al. 2010). People may also absorb BPA through the skin when touching objects containing the chemical. Although these sources of BPA exposure have not been well characterized, they could pose a greater health risk than oral ingestion of BPA because BPA that is inhaled or absorbed through the skin may spend more time circulating through the bloodstream in unconjugated form than BPA entering the body through the oral route and thus subject to first-pass elimination.

BPA is commonly used in thermal receipt papers, and although many people touch receipts regularly, cashiers handle them more frequently than most people. The NIEHS/NTP cashier study will measure BPA and BPA conjugates in cashiers' blood and urine samples before and after their work shifts. The study is expected to yield insights about the degree to which thermal receipt papers contribute to BPA exposure, although it will not determine whether the route of exposure is dermal absorption or oral ingestion (Liao and Kannan 2011).

NIEHS/NTP/NIOSH Occupational Exposure Study

Workers who directly handle BPA in places where BPA is produced or processed may be exposed to significantly higher levels of BPA than the general population (Wang et al. 2012). NIEHS/NTP and the National Institute for Occupational Safety and Health (NIOSH) have developed a study protocol to assess the routes and levels of exposure among such workers. The study will collect urine samples from 120 workers, as well as samples of BPA levels in the air and on workers' hands during their work shifts. The study aims to evaluate the levels of BPA exposure among occupationally-exposed people and to identify factors contributing to occupational exposures.

Discussion

NIEHS supports basic and translational research to understand the role of environmental exposures in human disease and dysfunction. Our focus is on improving human health. While investigator-initiated research is critical to this mission, in some cases a more strategic approach is warranted that stretches beyond—and maximizes the impacts of—individual grants. In the case of BPA, the hundreds of publications leading up to 2007 had not produced the necessary data risk assessors needed to inform conclusions and policy decisions about the health effects of BPA. To address the uncertainties and concerns surrounding BPA research, NIEHS developed an unprecedented, comprehensive research program that combines extramural grant funding with targeted intramural research efforts and overarching structures for collaboration to fill research gaps, solve controversies, and provide results that can inform regulatory decision-making.

While these efforts are still ongoing, several outcomes are already clear. First, the approach has yielded important research insights. NIEHS grantees and intramural researchers have published more than 100 papers since January 2010 that offer new data on BPA health effects for a wide range of doses and disease endpoints in both humans and animal models.

In addition, NIEHS's approach has demonstrated the value of workshops and collaboration in helping to focus a field, identify research needs, and resolve controversies. (See Supplemental Material, Table S4 for a summary of BPA-focused workshops organized by NIEHS.) The 2007 Chapel Hill consensus statement and 2008 NTP-CERHR report were instrumental in pinpointing critical research needs and spurred the institute to make targeted research investments; since then, the BPA Grantee Consortium and the CLARITY-BPA program have successfully used workshops to facilitate discussion among members of the BPA research community and develop shared solutions to address difficult research problems.

Furthermore, the BPA Grantee Consortium has demonstrated that members of the scientific community are eager to work together—even if it means adjusting their own approaches—in order to increase the collective impact of their work. Although unsolicited grantees were not officially funded as part of a formal consortium, most wholeheartedly embraced the consortium's goals. Following the establishment of the BPA Grantee Consortium, NIEHS developed two other research consortia—the Engineered Nanomaterials Grand Opportunity consortium, aimed at evaluating the health effects of exposure to nanomaterials, and the Deepwater Horizon Research Consortium, developed to coordinate research on the environmental health impacts of the 2010 Deepwater Horizon oil spill. Together, these consortia represent a new wave of collaboration in extramural research, often in concert with intramural efforts, at NIEHS. BPA grantees willingly shared technologies, data, and endpoints; animal researchers and epidemiologists were excited by the opportunity to work together to inform their research approaches and develop endpoints that could be measured in both animal and human studies. In addition, those applying for the Grand Opportunity funding agreed to make small changes to their protocols to provide data needed to fill research gaps. A detailed assessment of the results of the BPA Grantee Consortium, due to be completed in 2013, will document successes of this approach and identify areas for improvement.

Finally, NIEHS's BPA research program has received strong support from divisions across NIEHS and has been embraced by other federal agencies. Strong intra- and interagency collaboration will continue to be critical to the success of NIEHS's BPA research investments.

NIEHS's multipronged, collaborative approach to BPA research can provide lessons for other areas of environmental health. Future studies on environmental contaminants may benefit from an early focus on identifying data gaps and collaborative efforts to confront controversies (or prevent them before they arise). Fractured, uncoordinated research efforts can leave significant unanswered questions, impeding progress and making it difficult for risk assessors and regulators to interpret findings. In the future, perhaps earlier investments to identify needs and coordinate research efforts can save time and money, as well as improving our ability to protect human health.

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Figure Legend

Figure 1. Elements of the NIEHS BPA Research Program

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